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Risk factors for hoarseness and vocal symptoms in children



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*To Susanna,
without whom I would neither have started, nor finished.*

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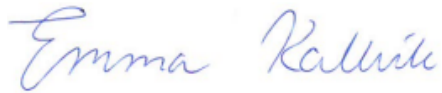
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Jakobstad, July 2018

A handwritten signature in blue ink that reads "Emma Kallvik". The script is cursive and fluid, with the first name "Emma" and the last name "Kallvik" written in a single continuous line.

Emma Kallvik

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- I Kallvik, E., Lindström, E., Holmqvist, S., Lindman, J., & Simberg, S. (2015). Prevalence of hoarseness in school-aged children. *Journal of Voice*, 29(2), 260.e1–19.
- II Kallvik, E., Putus, T., & Simberg, S. (2016). Indoor air problems and hoarseness in children. *Journal of Voice*, 30(1), 109–113.
- III Kallvik, E., Savolainen, J., & Simberg, S. (2017). Vocal symptoms and voice quality in children with allergy and asthma. *Journal of Voice*, 31(4), 515.e9–515.e14.
- IV Kallvik, E., Toivonen, L., Peltola, V., Kaljonen, A., & Simberg, S. (In press). Respiratory tract infections and voice quality in 4-year-old children in the STEPS study. *Journal of Voice*.

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AUTHOR'S CONTRIBUTIONS

Study I: The author had the main responsibility for the study. She planned the research project, collected the data, performed the data analyses, and wrote the manuscript.

Study II: The research project was planned in collaboration with Professor Putus. The author had the main responsibility for the data analyses and wrote the manuscript. Professor Putus collected the data within the scope of her other projects concerning indoor air quality and health.

Study III: The research project was planned in collaboration with Professor Savolainen. The author had the main responsibility for the data analyses and wrote the manuscript. Professor Savolainen was responsible for the data collection at Turku University Hospital.

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SAMMANFATTNING

Betydelsen av en effektiv talkommunikation ökar i samhället och i och med det också kraven på en välfungerande röst. De flesta barn som växer upp idag kommer i hög grad att vara tvungna att använda talkommunikation i sina framtida yrken och om rösten inte fungerar som den ska kan det här leda till svårigheter med att utföra sitt arbete. Rösten ger oss också ledtrådar om egenskaper hos den person som talar och om rösten är hes eller annars avvikande kan det leda till att åhörarna får en felaktig, till och med negativ, uppfattning om talaren. Alla heta barn behöver kanske inte få röstbehandling, men genom att veta mera om vilka faktorer som har ett samband med en hes röst skulle man dels kunna förebygga problem och dels inleda en intervention för att åtgärda de här faktorerna. Genom att veta mera om riskfaktorer blir det också möjligt att veta vilka barns röster som noggrannare borde följas upp.

Syftet med den här avhandlingen var att undersöka förekomsten av heshet och olika röstsymptom hos fyra olika grupper barn och att identifiera möjliga riskfaktorer som har en koppling till heshet och röstsymptom.

Deltagarna i både studie I och studie II var 6 – 9 år gamla. Deltagarna i studie I var en normalpopulation på 217 barn och deltagarna i studie II var 1857 barn som antingen deltog i en pedagogisk verksamhet i en byggnad som hade inomhusluftsproblem på grund av en fuktskada eller hörde till kontrollgruppen. Deltagarna i studie III var 108 barn som alla hade allergi och/eller astma. Barnen var mellan 0:9 och 17:1 år gamla. I studie IV var deltagarna 4-åriga barn som deltog i den mångprofessionella kohortstudien Steps to the Healthy Development and Well-being of Children (the STEPS study).

I alla fyra studier användes frågeformulär som fylldes i av föräldrarna. I studie I fyllde också lärarna i ett kort frågeformulär och i den bedömdes barnens röster perceptuellt av åtta bedömare som utbildats specifikt för uppgiften. I studie IV användes förutom frågeformulär också en dagbok där föräldrarna fyllde i hälsorelaterad information. Information om sjukhusvistelser och läkarbesök erhöles från sjukvårdsdistriktets patientdataregister. Under de två första levnadsåren togs näsprov i början av alla luftvägsinfektioner för att identifiera vilket virus som orsakat infektionen.

Heshetsprevalensen i normalpopulationen i studie I var 12 % och förekomsten av ofta förekommande röstsymptom 6 %. Av barnen med allergi och/eller astma hade 18,2 % ofta förekommande röstsymptom. Av de barn som deltagit i pedagogisk verksamhet i en byggnad med inomhusluftsproblem på grund av en allvarlig fuktskada var 9,3 % heta varje vecka eller oftare. Resultaten från studie II visade att inomhusluftsproblem på grund av fuktskada bidrar till en oftare förekommande heshet. Hosta verkade ha en koppling både till röstsymptom och till hes röstkvalitet. I studie II var både slemhosta och torr hosta prediktorer för ofta förekommande heshet och i studie III hade långvarig hosta ett signifikant samband med ofta förekommande röstsymptom. Riskfaktorer som hade en koppling till heshet och röstsymptom var: nästäppa, luftvägsallergi, kraftig röstanvändning som baby (för flickor), att vara det yngsta syskonet (för pojkar) och antalet luftvägsinfektioner som lett till sjukhusvistelse.

Baserat på resultaten i den här avhandlingen verkar hälsotillstånd som leder till hosta ha ett samband med heshet och ofta förekommande röstsymptom. Eftersom hosta är ett vanligt symptom på luftvägsinfektion så kan man också anta att en stor del av de som haft luftvägsinfektioner som lett till sjukhusvistelse också haft hosta. Gemensamt för alla de riskfaktorer som identifierats i avhandlingen är att de kan påverka stämbanden negativt

genom den mekaniska påfrestningen som de innebär. Hur exakt denna påverkan sker behöver dock utredas vidare. Baserat på resultatet av den här avhandlingen skulle det vara viktigt att utreda och behandla barns hosta. Det skulle även vara viktigt att uppmärksamma röstsymptom hos barn som har astma och allergi för att vid behov kunna skicka dem vidare till röstbehandling. Riskfaktorerna som identifierats i avhandlingen kunde med fördel inkluderas i de bakgrundsfrågor som ställs då ett barn är hest eller har röstsymptom.

SUMMARY

The importance of a well-functioning voice is increasing for the working population as more and more persons are working in voice demanding professions. Most of the children growing up today will depend on their voice to perform in their future professions, and if the voice does not function as expected, this could interfere with their ability to perform at work. Besides being a tool, the voice quality also gives us clues about the person speaking. If the voice is hoarse or otherwise affected, this could lead to false assumptions about the speaker. It might not be necessary to provide direct voice therapy to all hoarse children, but knowing who is at risk could help in deciding which groups would benefit from voice screening. Knowledge about potential risk factors for hoarseness or other vocal symptoms could also be used for prevention, or as a first step in an intervention.

The aim of the present thesis was to investigate the prevalence of hoarseness and other vocal symptoms in four different groups of children and to identify possible risk factors for hoarseness and other vocal symptoms.

Both the participants in Study I and in Study II were 6 – 9-year-olds. In Study I, they were a normal population of 217 children and in Study II, they were 1857 children that either had attended an educational setting in a building with indoor air problems due to moisture damage or were part of a control group. The participants in Study III were a group of 108 children with allergy and/or asthma, aged 0:9 to 17:1 years. In Study IV, the participants were a normal population of 489 children that participated in the multidisciplinary cohort study Steps to the Healthy Development and Well-being of Children (the STEPS study).

In all four studies, data were collected with questionnaires that were filled in by the parents of the participating children. In the first study, teacher questionnaires and perceptual evaluation by eight trained listeners was also used. In Study IV, health related information was recorded in a diary filled in by the parents and data on hospitalizations and physician visits were obtained from the electronic registry of the hospital district. At the onset of a respiratory tract infections during the first two years of life, nasal swabs were taken for virus identification.

The prevalence of hoarseness in the normal population of children was 12 % and the prevalence of frequently occurring vocal symptoms was 6 %. The children with allergy and/or asthma had a prevalence of frequently occurring vocal symptoms of 18.2 %. Of the children who had attended an educational setting in a building with indoor air problems due to severe moisture damage, 9.3 % were hoarse every week or more often. The results of Study II showed that indoor air problems due to moisture damage contribute to a more frequently occurring hoarseness. Cough seemed to be connected to both vocal symptoms and hoarse voice quality. In Study II, both phlegm cough and dry cough were significant predictors for frequently occurring hoarseness. In Study III, prolonged cough had a significant connection to frequently occurring vocal symptoms. Other risk factors that had a connection to hoarseness and frequently occurring vocal symptoms were: nasal congestion, inhalant allergy, heavy voice use as an infant (for girls), being the youngest sibling (for boys), and the number of respiratory tract infections that have led to hospitalization.

Based on the results of this thesis, health conditions that cause cough seem to have a connection to hoarseness and frequently occurring vocal symptoms. Because cough is a common symptom of respiratory tract infection, it is also reasonable to assume that the children that have been hospitalized because of a respiratory tract infection could have had cough. The common feature of all risk factors identified in this thesis is that they subject the

vocal folds to mechanical strain. The exact mechanism for this needs to be investigated further. Based on the results of this thesis, it would be recommendable to elucidate and treat cough in children. It would also be important to screen children with allergy and/or asthma for vocal symptoms. The risk factors identified in this thesis could be included in the pediatric voice anamnesis.

1. Introduction

The interest in children's voice quality and vocal symptoms is no novelty. For example, in 1915, Weinberg investigated hoarseness in Swedish school children. When reading Weinberg's research, one is struck by how similar Weinberg's thoughts and discussion on the etiology of hoarseness is to the current model of explanation. Weinberg talks about the dangers for the child voice in the school and home environment and the impact of vocal behavior, especially in boys. These thoughts echo in the modern child voice research where environment, personality, and health are still relevant when investigating the background of hoarseness and other vocal symptoms. Even though the interest in child voice is old, the ever increasing demands set upon the voice today makes this field of research even more important than before. While many professions are automatized, service and personal counseling still remains professions that require a live person doing the work. Neither assisting people at help desks or in call centers, coordinating operations in dispatch centers, providing therapy, nor teaching or preaching can be done by machines, but has to be performed by a human being with a clear voice.

In children, risk factors for hoarseness that have been identified in previous studies are personality and temperament, health related factors, and environmental factors. Personality and temperament factors have been described in both positive and negative terms. The results of a study by D'Alatri et al. (2015) showed that ADHD is a possible risk factor for childhood vocal nodules and a study by Green (1989) showed that children with vocal fold nodules scored higher on acting out, distractibility, disturbed peer relations, and immature behaviors. Roy, Holt, Redmond, and Muntz (2007), on the other hand, found that children with vocal fold nodules were significantly more outgoing and extroverted, but not aggressive, attentional, or impulsive. Personality and temperament factors will only be briefly mentioned in this thesis, and the main focus will be on health and environmental factors.

What we perceive as hoarseness is caused by turbulence and air loss due to incomplete glottic closure, or by irregular vibrations of the vocal folds (Eysholdt, Rosanowski, & Hoppe, 2003). Voice disorders in adults, especially in those who have voice demanding professions, has been thoroughly investigated (Cutiva, Vogel, & Burdorf, 2013; Da Costa, Prada, Roberts, & Cohen, 2012; Hagelberg & Simberg, 2015; Russell, Oates, & Greenwood, 1998; Smith, Lemke, Taylor, Kirchner, & Hoffman, 1998) and the majority of patients in the voice clinic are adults (Martins et al., 2016). Children, on the other hand, have in Finland not yet found their way to treatment to the same extent as adults (Kallvik & Simberg, 2016). The results of a questionnaire study answered by members of the Finnish association for speech-language pathologists showed that notably fewer children than would be expected based on the results of prevalence studies see a speech-language pathologist due to voice complaints (Kallvik & Simberg, 2016). The reason for this could be that the children might not actively communicate their discomfort to the parents, and therefore not find their way to the voice clinic. Less treatment was also offered to children than to adults, generally 2–5 visits compared to 6–10 visits (Kallvik & Simberg, 2016). Compliance issues in pediatric voice patients might be a reason for this.

Children with dysphonia seem to, contrary to commonly held beliefs, be aware of their voice and concerned by their voice problems. In a study by Verduyck, Remacle, Jamart, Benderitter, and Morsomme (2011), the 6 – 13-year-old children with dysphonia expressed that they felt frustrated, angry, embarrassed, and dissatisfied with their voice, and was

asked questions because of their voice significantly more often than the children with typical voices. In a study by Connor et al. (2008), 50 % of the younger children, 40 % of the school-children, and 80 % of the adolescents were sad, angry, embarrassed, and frustrated by their voices. On the other hand, some of the children interviewed by Verduyck et al. (2011) expressed mixed feelings about their voices, describing their voice quality in negative words, but still expressing that they liked it.

Not only the children themselves might react negatively to the hoarse voice quality, but the hoarse voice quality can also elicit negative reactions from people in the environment. In a perceptual evaluation by other children of the same age as the participants (Lass, Ruscello, Stout, & Hoffman, 1991), children with voice disorders were, based on their voice, assigned more negative traits than the voice healthy control group. According to Gobl and Chasaide (2003), different voice qualities play a role in communicating affective states. If the voice quality is altered due to other reasons than emotion, this could lead to false conclusions about the speaker's emotional state. The results of a study by Ma and Yu (2013) showed that primary school teachers, speech-language pathology students and general university students all rated children with voice disorders less favorably than children with healthy voices. It is remarkable that even speech-language pathology students that have been trained in vocology have negative attitudes towards the children with voice disorders.

Adults are also viewed more negatively if they have a hoarse voice (Allard & Williams, 2008; Amir & Levine-Yundof, 2013; Lallh & Rochet, 2000). The results of a study by Lallh and Rochet (2000) showed that adult women with voice and resonance disorders were perceived more negatively than women with healthy voices, regardless of whether the listeners had received information on voice disorders prior to the listening session or not. Similar results were obtained in a study by Allard and Williams (2008) where a male actor enacted hoarseness as well as some other speech and communication disorders. He was rated more negatively when he made his voice hoarse than when he did not enact any disorder (Allard & Williams, 2008). Additionally, the results of a study by Altenberg and Ferrand (2006) showed that the degree of negative reactions in listeners increased with the degree of hoarseness. Apart from the negative reactions by persons in the environment, there is also a risk that hoarse children grow up to become hoarse adults whose life and career choices could be restricted by the hoarseness. Not all cases of voice complaints and dysphonia resolve during puberty, not even for those who have received intervention (De Bodt et al., 2007; Mackiewicz-Nartowicz et al., 2014). This is especially apparent for girls (De Bodt et al., 2007; Mackiewicz-Nartowicz et al., 2014). If the voice quality is not good enough for the career path that the young person would like to pursue, this could stop the person from enrolling in the education and, in the future, from performing well in the profession that he or she would have preferred.

1.1 Definitions and terminology

There are many different views on the defining features of a voice disorder. At least three different viewpoints can be distinguished among the definitions: the functional, the comparative, and the symptom based. The functional viewpoint focuses on the relation of the voice function to the demands set upon it. These definitions are, for example, that a voice disorder is "any time the voice does not work, perform, or sound as it normally should, so that it interferes with communication" (Roy, Merrill, Thibeault, Parsa, Gray, &

Smith, 2004, p. 283) and that the voice does not fulfill the requirements set upon it (Vilkman, 2004).

In comparative definitions, a voice disorder is defined in relation to a voice quality that is regarded as normal or typical. One such comparative definition is that “a voice disorder exists when the quality, pitch, loudness, or flexibility differs from the voices of others of similar age, sex, and cultural group” (Aronson, 1985, p. 7). A definition that combines the comparative and the symptom based approach is Olson-Ramig and Verdolini (1998) who are defining a voice disorder as: “an abnormal pitch, loudness and/or vocal quality resulting from disordered laryngeal, respiratory and/or vocal tract functioning” (p. S101). One commonly used symptom based definition (e.g. Hagelberg & Simberg, 2015; Ohlsson, Andersson, Södersten, Simberg, & Barregård, 2012; Sala, Laine, Simberg, Pentti, & Suonpää, 2001; Simberg, Sala, Vehmas, & Laine, 2005; Simberg, Santtila, Soveri, Varjonen, Sala, & Sandnabba, 2009) is that a voice disorder is present when you experience two or more of a set of vocal symptoms (throat clearing/coughing, voice becomes strained or tires, voice becomes low/hoarse, sensation of pain or lump in the throat, voice breaks, difficulty in being heard, aphonia) every week or more often.

The focus of this thesis is on voice quality and vocal symptoms. Variations in resonance are not included, and variations in pitch will only be mentioned as a vocal symptom among others (the voice becomes low or hoarse). To facilitate the communication of our main focus to the parents and teachers who were important collaborators in the data collection, we chose to use the word hoarseness as a general term in the questionnaires. Different variations of the concept of hoarseness (e.g. chronic hoarseness or husky and hoarse voice) has been used as the term in many previous child voice studies (Akin Şenkal & Çiyiltepe, 2013; Block & Brodsky, 2007; Duff, Proctor, & Yairi, 2004; McKinnon, McLeod, & Reilly, 2007; Sederholm, 1995; Sederholm, McAllister, Dalkvist, & Sundberg, 1995; Sederholm, McAllister, Sundberg, & Dalqvist, 1993; Silverman & Zimmer, 1975). The results of Sederholm et al. (1993) indicated that hoarseness as a concept corresponded well to the human perceptual system for voice quality. The results also showed that breathiness, hyperfunction and roughness were key parameters underlying hoarseness (Sederholm et al., 1993).

1.2 Prevalence of voice disorders

The most common diagnosis for children with dysphonia in a treatment seeking population studied by Martins et al. (2016) was vocal nodules, followed by vocal cysts, and acute laryngitis. For adults, the most common diagnoses varied depending on age group. Functional dysphonia was most common in younger adults, and presbyphonia was most common in adults that were over 60 years old. Younger adults were also commonly diagnosed with nodules and polyps, while Reinke’s edema and acid laryngitis were common in adults over 40 (Martins et al., 2016). In a retrospective study of a claims database in the US, the point prevalence rate of dysphonia in persons of all ages was 0.98 % (Cohen, Kim, Roy, Asche, & Courey, 2012). The prevalence rate was lowest in children and adults under 30, and increased thereafter with age (Cohen, Kim, Roy, Asche, & Courey, 2012). Cohen et al. (2012) do, however, point out that not everyone with dysphonia seeks help, and that the actual rate could be higher. In studies with adult participants only, voice disorders are reported in around 6 % (Roy, Merrill, Thibeault, Gray & Smith, 2004; Roy, Merrill, Gray & Smith, 2005). In adults, more women than men are diagnosed with voice disorders and

laryngeal pathologies both in the general population (Roy, Merrill, Thibeault, Parsa et al., 2004), in help-seeking populations (Cohen et al., 2012; Coyle, Weinrich, & Stemple, 2001) and in different occupational risk groups (Da Costa et al., 2012; Hagelberg & Simberg, 2015; Russell et al., 1998; Smith et al., 1998).

Among children, the prevalence reported varies between 0.12 % (McKinnon et al., 2007) and 28 % (Koivusaari, 1998) and the studies have included between 40 (Curry, 1949) and 10,425 participants (McKinnon et al., 2007). In children, the gender distribution is generally the other way round with more boys than girls having a voice disorder (Carding, Roulstone, Northstone, & the ALSPAC Study Team, 2006; McKinnon et al., 2007; Sederholm, 1995), although some results indicate that a gender difference would not be present in younger children (Duff et al., 2004). The explanation for the variation in reported prevalence can be the use of different methodology and different definitions of what a voice disorder is. McKinnon et al. (2007) used a multiple-stage method beginning with an information session for principals and learning support teachers about the data collection, after which the principals and learning support teachers trained all teachers in their school how to collect the data. After this, the teachers supplied information on all their pupils and identified the children in their class that filled the descriptions provided. These reports were then reviewed and corroborated by the learning support teacher and if a child was reported to have a speech or communication disorder, the teacher report was to be corroborated by a speech-language pathologist. As a last stage, a special needs advisor reviewed the results. The prevalence study by Sederholm (1995) was on the other hand based on perceptual evaluations of recorded voice samples and a questionnaire. The results of Sederholm (1995) showed a prevalence of 14 %. Previous prevalence studies along with the definitions the authors used are listed in Table 1.

Table 1

A brief review of some previous studies of prevalence of voice problems in children

Author	Year	Age group	N	Participants	Prevalence (%)	Definition of voice disorder
Weinberg	1915	7–14	800	boys and girls	26.9	Hoarseness
Curry	1949	10	40	boys	55	Husky and hoarse voice
Curry	1949	14	40	boys	80	Husky and hoarse voice
Baynes	1966	6–12	1012	boys and girls	7.1	Hoarseness
Silverman & Zimmer	1975	5–14	162	-	23.4	Chronic hoarseness
Powell et.al.	1989	6–10	203	boys and girls	23.9	Voice disorder
Koivusaari	1998	7–13	1694	boys and girls	28	Phonation and resonance disorder
Sederholm	1995	10	205	boys and girls	14	Hoarseness
Duff et al.	2004	2–6	2445	boys and girls	3.9	Hoarseness
Carding et al.	2006	8	7389	boys and girls	6	Atypical voice
McKinnon et al.	2007	5–12	10425	boys and girls	0.12	Husky and hoarse voice
Tavares et al.	2011	4–12	2000	boys and girls	6.15	Parent report: voice frequently or permanently changed
					11.4	Perceptual evaluation: Grade=2

1.3 Measuring voice disorders

Perceptual evaluation of voice means that a listener rates a voice in relation to their own internal standards of how a normal voice should sound (Fex, 1992). Perceived voice quality can be measured on different types of scales and the most commonly used are categorical rating scale, equal-appearing interval scale and visual analogue scale (VAS) (Kreiman, Gerratt, Kempster, Erman, & Berke, 1993). On a categorical rating scale, the alternatives are dichotomous or unordered categories as for example strained or rough. An equal-appearing interval scale consists of numbers that are assumed to be equidistant from each other. A VAS is usually a 100 mm undifferentiated line on which the listener marks his or her rating (Kreiman et al., 1993). The visual analogue scale has been developed for measuring subjective phenomena, such as pain or mood states (Wevers & Lowe, 1990). Originally, the VAS was intended for the evaluation of individuals by raters, but has later also been used for self-rating purposes (Wevers & Lowe, 1990). In previous child voice studies on hoarseness (Sederholm, 1995; Sederholm, McAllister, Sundberg, & Dalkvist, 1993), the expert listeners used a VAS in the perceptual evaluation of the voice samples.

In a review by Kreiman et al. (1993), no clear relationship could be seen between the listeners' experience and inter-rater and intra-rater reliability. According to the results of a study on the effect of experience on perceptual evaluation by Eadie et al. (2010), experienced and inexperienced listeners' perceptual voice evaluations were very similar, reflected by a strong significant relationship between their perceptual voice evaluations. In contrast, the self-evaluations of persons with dysphonia were in less agreement with the experienced and inexperienced listeners (Eadie et al., 2010). This could indicate that the persons had become accustomed to how their own voices sounded. Based on this, it seems that external raters are more reliable when doing perceptual voice evaluation.

The benefits of perceptual evaluation above acoustic analysis is the ability of the human ear to ignore interfering factors such as background noise or a highly variable fundamental frequency, and the ability to rate connected speech. Additionally, perceptual evaluation is both convenient, and economical to use (Kent, 1996). The negative aspects of perceptual evaluation is that the listener's internal representations of what is being judged can differ, different scales are used which makes it harder to compare the results of different studies, and different perceptual dimensions are not rated with the same reliability (Kent, 1996).

In a review of studies on parent and child agreement on different types of questions in health-related quality of life (HRQOL) questionnaires, the results were inconclusive with five studies of 13 showing a higher agreement on concrete, observable characteristics, while the results of four studies showed higher agreement for psychosocial characteristics (Upton, Lawford, & Eiser, 2008). A later study, not included in the review, showed the level of agreement was higher in the more observable dimensions (Rajmil, Rodríguez López, López-Aguilà, & Alonso, 2013). The answer agreement between parent and child on HRQOL questionnaires is generally fair to good (Brunner et al., 2004), but diminishes as the child gets older (Rajmil et al., 2013). Other factors affecting the degree of agreement on HRQOL questionnaire are if the child already has a diagnosis and whether or not he or she is part of a help-seeking or a normal population (Upton et al., 2008). The results of a study by Cohen and Wynne (2015) showed that on matters concerning voice-related quality of life, children with dysphonia aged 4–15 years were able to evaluate the impact of their dysphonia on their quality of life. The evaluations by the children were compared with the parent's evaluations and the results showed that the evaluations did differ in aspects such as the physical functioning and social-emotional impact of the dysphonia (Cohen & Wynne, 2015).

1.4 Structure and development of the vocal tract

The structures located between the vocal folds and the lips are commonly referred to as the vocal tract (Fitch & Giedd, 1999). Adult vocal folds have a layered structure with the muscle located at the core of the vocal folds (Hirano, 1981). The muscle is covered by the three-layer lamina propria (Hirano, 1981) which is a connective tissue layer with an extracellular matrix consisting of fibrous proteins, interstitial proteins, lipids, and carbohydrates (Gray, Titze, Alipour, & Hammond, 2000). The lamina propria is, in turn, covered by the epithelium that is at the surface of the vocal folds. The fibrous proteins elastin and collagen in the lamina propria contribute to the elasticity and stability of the vocal folds (Chan, Fu, Young, & Tirunagari, 2007). The deep layer of the lamina propria has a high collagen content that gives the vocal folds tensile strength while the intermediate layer with its high elastin content gives the vocal folds elasticity (Hammond, Gray, & Butler, 2000) and allows the tissue to deform and return to its original shape (Gray et al., 2000). The properties of

the intermediate and deep layers of the lamina propria limits the range of movement of the vocal folds, and thereby protects them from excessive stretch (Titze, 1994). The epithelium acts as a protective barrier to the underlying layers (Levendoski, Leydon, & Thibeault, 2014).

The anatomical proportions in a child differ from the adult proportions, and the child laryngeal tract is not just a smaller version of an adult larynx (McAllister & Sjölander, 2013). In young children, the ratio between the membranous and the cartilaginous part of the vocal folds is different than in adults (Sapienza, Ruddy, & Baker, 2004). The cartilages are softer and the microstructure of the vocal folds is different from the adult microstructure. In adults, the lamina propria consists of three layers while in children, these layers have not yet matured. At birth, the vocal fold lamina propria seems to consist of only one layer (Boseley & Hartnick, 2006; Sato, Hirano, & Nakashima, 2001) and contain only traces of immature elastic fibers (Moore & Thibeault, 2012; Sato et al., 2001). At 5 months, two layers are already distinguishable (Boseley & Hartnick, 2006). The structural development is reflected by a subsequent fine tuning of the infant cry (Fuamenya, Robb, & Wermke, 2015).

In a multiple case study of excised child larynges of different ages, the proportions of the different layers in the lamina propria approximated the adult proportions in the 5 year old larynx even though the deep layer of the lamina propria was hard to detect (Boseley & Hartnick, 2006). In a 6-year old child, the vocal tract structures are 65–85 % of the adult size and approximates the full-grown size (Vorperian, Kent, Lindstrom, Kalina, Gentry, & Yandell, 2005). Some structures get closer to their adult size earlier, for example the hard palate, mandible and pharynx, while others, as the tongue, continues to grow and the larynx and hyoid bone lowers considerably after age 6 (Vorperian et al., 2005).

At age 7, three layers are distinguishable in the lamina propria (Hartnick, Rehbar, & Prasad, 2005) and the proportions of the superior lamina propria to the rest of the layers start to resemble the adult vocal folds (Boseley & Hartnick, 2006). The amount of elastin fibers in the vocal folds also increases throughout the development as the three layer structure develops (Moore & Thibeault, 2012). A typical vocal ligament, i.e. the intermediate and deep layers of the lamina propria, is not present before early adolescence, around the same time as the voice mutation starts (Hartnick et al., 2005). The maturation and development of the vocal folds continue throughout puberty (Hartnick et al., 2005) and the larynx is usually not fully grown until the age of 20 or 21 (Spiegel, Sataloff, & Emerich, 1997).

Young children have lower levels of the stabilizing collagen in the deep layers of the lamina propria (Hammond et al., 2000) and less resiliency providing elastin fibers throughout the vocal folds (Moore & Thibeault, 2012). This, combined with the immature layer structure means that the vocal folds are able to vibrate with more force (Hirano & Kurita, 1986) and make contact at a higher velocity (Patel, Donohue, Lau, & Unnikrishnan, 2013).

Although it is possible to perceptually distinguish prepubertal girls from prepubertal boys (Amir, Engel, Shabtai, & Amir, 2012; Perry, Ohde, & Ashmead, 2001), there does not seem to be any major gender differences in laryngeal and airway anatomy before puberty. The vocal tract structures grow at a similar rate (Vorperian et al., 2005), and the vocal tract length is not significantly different when comparing prepubertal girls with prepubertal boys (Fitch & Giedd, 1999). Vocal tract length is instead correlated with body size (Fitch &

Giedd, 1999). The size of the glottis and cricoid cartilage is also more related to age, height, and weight than to gender (Dalal et al., 2009).

When selecting participants for the studies in this thesis, it was desirable that they had reached a sufficiently mature stage of vocal fold development, but still not entered puberty. The onset of puberty differs between different groups of children. According to Herman-Giddens et al. (1997), the average age for onset of puberty for girls of Caucasian origin in the United States was 10 years and slightly lower, between 8 and 9 years, for girls of African American origin. The results of a Swedish study, showed an average age for onset of puberty of 11.1 for girls years and 12.1 years for boys (Persson et al., 1999). At the age of puberty, the voice quality of a child is to some extent affected by the voice mutation. The results of a study by Harries, Walker, Williams, Hawkins, and Hughes (1997) showed that the largest voice changes in boys occur during the middle stages of puberty and not at onset.

1.5 Health related risk factors

For the purpose of this thesis, health related risk factors are defined as the intrinsic factors related to the state of health of a person that can have an effect on the voice. Factors that can affect the epithelial barrier of the vocal folds are for example gastroesophageal reflux disease (GERD), and the inflammatory mediating histamine (Levendoski et al., 2014). Injury to the epithelium can also occur due to intense use of the vocal fold (Levendoski et al., 2014).

Epithelium in other parts of the body is damaged by viral and bacterial infections, and the same effect could be hypothesized to be found in the vocal fold epithelial barrier (Levendoski et al., 2014). Asthma is a chronic respiratory disease in which inflammation and narrowing of small airways causes attacks of impaired breathing (Akinbami, Moorman, & Liu, 2011) and the symptoms are, among others, cough and sputum production (Stirling & Chung, 2001). Besides the symptoms, some medicines that are used for treating asthma can also have a negative effect on the voice quality (Abaza, Levy, Hawkshaw, & Sataloff, 2007; Buhl, 2006; Ihre, Zetterström, Ihre, & Hammarberg, 2004). In adults, allergy seems to have a connection to vocal symptoms (Ohlsson, Drevsäter, Brynnel, & Johansson, 2015; Simberg, Sala, Tuomainen, & Rönnemaa, 2009) and inhalant allergy can cause allergic laryngitis which affects the voice (Jackson-Menaldi, Dzul, & Holland, 2002). A healthy, undamaged, layered vocal fold structure is important for an effective phonation, and a damaged structure could lead to an altered voice quality or vocal symptoms.

1.5.1 Respiratory tract infections

The duration of a respiratory tract infection depends on how old the child is and if he or she attends day care, but is usually 5–6 days (Byington, Wilkes, Korgenski, & Sheng, 2015; Heikkinen & Järvinen, 2003; Monto & Sullivan, 1993). A common symptom of respiratory tract infection is cough (West, 2002; Widdicombe, 1995). Age and gender influences the susceptibility for respiratory tract infections. Most respiratory tract infections are found in children up to the age of four (Monto, 2002) and girls are more likely than boys to acquire some types of respiratory tract infections (Karevold, Kvestad, Nafstad, & Kværner, 2006).

Respiratory tract infections can be caused by both viruses and bacteria (West, 2002). A virus infection can also facilitate a secondary bacterial infection through weakening of the epithelial barrier of the vocal folds (Sajjan, Wang, Zhao, Gruenert, & Hershenon, 2008). In

a study by Mäkelä et al. (1998) of adults with common cold, the results showed that 69 % of the cases of common cold had viral etiology. The most common viral etiology for respiratory tract infections in children is rhinovirus (Chu et al., 2016; Jacobs, Lamson, St George, & Walsh, 2013). Different viruses peak at different times of the year, for example there is a respiratory syncytial virus peak in winter to early spring, parainfluenza virus peaks in late autumn to winter, and rhinoviruses peak in the fall and spring (Monto, 2002).

Environmental factors can impact the susceptibility for respiratory tract infections. The results of a study by Karevold et al. (2006) showed that moisture damage in the home increased the risk for otitis media, tonsillopharyngitis, bronchitis, and pneumonia. Children in day care outside of home have more respiratory tract infections than children in home care (Uhari, Mäntysaari, & Niemelä, 1996; Wald, Guerra, & Byers, 1991). They also have a higher risk of more severe respiratory tract infections (Uhari et al., 1996; Wald et al., 1991).

1.5.2 Allergy

According to a review by Roth and Ferguson (2010), it is likely that inhalant allergy is associated with dysphonia. When screening for inhalant allergy, common allergens tested for are pollens, mold, dust mites, animal dander and cockroach (Krouse & Mabry, 2003). Strachan, Harkins, Golding, and the ALSPAC Study Team (1997) used the definition that inhalant allergy is being allergic to one or more of the allergens cat, pollen and dust. The results of a study by Baatenburg de Jong, Dikkeschei, and Brand (2011) showed that boys were more commonly sensitized to one or more allergens than girls. With increasing number of allergens, the proportion of boys increased as well (Baatenburg de Jong et al., 2011).

The results of a study by De Bodt et al. (2007) showed that girls with allergy who had voice complaints as children were more likely to have voice complaints after puberty as well. In a study by Simberg, Sala, et al., (2009), the results showed that young adult participants with inhalant allergy reported significantly more vocal symptoms than participants without allergy. In adults, the result of a study by Randhawa, Nouraei, Mansuri, and Rubin (2010) indicated a connection between inhalant allergy and vocal dysfunction measured with the Voice Handicap Index (VHI). Hidden inhalant allergies can also be the cause for recurring laryngitis or vocal fold edema (Jackson-Menaldi, Dzul, & Holland, 1999).

The results of two studies (Millqvist et al., 2008; Ohlsson et al., 2015) showed that persons allergic to pollen experienced more vocal symptoms (measured with VHI) than the control group during the birch pollen season. It is possible to alleviate vocal symptoms with immunotherapy (Cohn, Sataloff, & Branton, 2001; Simberg, Sala et al., 2009), but not with symptomatic treatment of allergic rhinitis (Cohn et al., 2001). This suggests that the allergic reaction itself, not only the symptoms, is of importance in the development of the vocal symptoms.

If inhalant allergy has been ruled out as the cause of dysphonia or airway symptoms, food allergy could also be suspected (Dixon, 1999; James, 2003). An allergic reaction to food is caused by abnormal immune responses to food proteins (Cianferoni & Spergel, 2009) and can lead to dysphonia because of thick mucus production and irregular glottic edge edema (Dixon, 1999). Depending on geographical location, the frequency of different food allergies vary (Cianferoni & Spergel, 2009). The prevalence of self-reported food allergy in children has been estimated to be 6.86 % in Europe (Nwaru et al., 2014) and 8 % in the United States (Gupta et al., 2011). In some allergic children with asthma, it is also possible that ingestion of food that the child is allergic to results in an increased airway

hyper responsiveness even though no direct allergic reaction to the food matter is present (James, 2003).

1.5.3 Asthma

In the International Study of Asthma and Allergies in Childhood, asthma is defined as having had wheezing or whistling in the chest during the past 12 months (Innes Asher et al., 2006). Another definition in a consensus statement by Warner et al. (1989) was that asthma is “episodic wheeze and/or cough in a clinical setting where asthma is likely or other rare conditions have been excluded” (p. 1065). Symptoms of asthma are cough, wheeze, shortness of breath, chest tightness and sputum production, usually varying during the day and worsening during the night (Stirling & Chung, 2001). The prevalence of asthma in Nordic children is estimated to be around 10 % in 6–7 year-olds in Sweden and 13–19 % in 13–14 year-olds in Sweden and Finland (Innes Asher et al., 2006). In a previous study, persons with asthma scored significantly higher on a perceptual evaluation of grade, roughness, and breathiness (Dogan, Eryuksel, Kocak, Celikel, & Sehitoglu, 2007). They also had shorter maximum phonation times (Dogan et al., 2007).

Inhaled corticosteroids (ICS) is a common treatment for asthma (Urbano, 2008). Common side effects of ICS are, among others, hoarseness, pharyngitis, and reflex cough (Buhl, 2006). The results of a study by Ihre et al., (2004) showed that persons with asthma who were using ICS experienced hoarseness, throat clearing, a lump in the throat, loss of voice, and throat pain. The relation between inhalation of corticosteroids and having voice problems was significant in the study by Ihre et al. (2004). On the other hand, the incidence of some local side effects depend more on the device used and less on the drug according to Dubus et al. (2001). In children using ICS, hoarseness was experienced as a side effect by 14.1 %, and dysphonia by 11.1 % (Dubus et al., 2001). Dubus et al. (2001) did not specify the distinction between hoarseness and dysphonia in the article. Hoarseness related to inhaled steroids were in a study by Lavy, Wood, Rubin, and Harries (2000) seen in the throat as mucosal changes, apposition problems, and supraglottic hyperfunction.

In the study by Ihre et al. (2004), equally many women and men had voice problems in the population with asthma, unlike in the general population, and the connection between voice problems and ICS was equally strong for both genders. Other correlates for voice problems in the study by Ihre et al. (2004) were degree of asthma trouble, dose, and acid regurgitations.

1.5.4 Cough

In a study by Block and Brodsky (2007), cough was reported in 30 % of the children who had visited a pediatric otolaryngologist with hoarseness among their symptoms. Throat clearing was reported in 28 %. Among the children in the study by Block and Brodsky (2007), more boys than girls presented with hoarseness (ratio 1.7:1).

Cough is triggered by stimulus in the upper aerodigestive tract (Altman et al., 2002). The stimuli can be chemical or mechanical irritants, inflammatory mediators, and certain disease states (Altman et al., 2002). The receptors towards the larynx are more mechanosensitive while the receptors in the bronchial airway are more chemosensitive. The stimulus excites sensory receptors that mediate the information to the brainstem at the level of the nucleus tractus solitarius (Altman et al., 2002). The brain will then start a sequence of events, starting with a deep inspiration, followed by glottic closure and

relaxation of the diaphragm. After this, the thoracic muscles contract to increase airway pressure and the trachea narrows followed by opening of the glottis and an explosive increase in airway flow rate that is designed to expel mucus or foreign bodies from the airways (Altman et al., 2002). The motor neurons responsible for this are nucleus ambiguus and the nucleus retroambigualis located in the ventral respiratory group (Altman et al., 2002).

Cough can serve as an indicator of an illness or as a defensive mechanism (Irwin & Curley, 1991). Depending on the purposefulness of the cough, different treatment options are considered, either antitussive, to eliminate cough, or protussive, with the purpose of making the cough more effective. The treatment is preferably directed primarily at the underlying disease (Irwin & Curley, 1991). Antitussive treatment is important to reduce the repeated laryngeal trauma caused by the cough (Altman et al., 2002). Cough also impacts the health-related quality of life in the persons affected (Brignall, Jayaraman, & Birring, 2008).

Cough has a multifactorial background and can be acute or chronic. The cough is categorized as chronic if it lasts for more than three weeks (Irwin et al., 1998). Common causes of chronic cough according to Altman et al. (2002) are cigarette smoking, post-nasal drip, GERD, chronic bronchitis and asthma. The role of post-nasal drip as a cause of cough in children has though been questioned (Kemp, 2006). If a clear laryngeal, tracheal or rhinologic pathology is absent, other causes of cough as vagal neuropathy and paradoxical vocal fold motion can be considered (Altman et al., 2002). GERD causes cough through two different mechanisms: acid irritation triggering cough through the vagus nerve or through microaspirations of esophageal content (Altman et al., 2002). Although there are numerous symptoms of GERD, many persons can have a clinically silent GERD with no other symptoms than cough (Harding & Richter, 1997).

Coughing and throat clearing can be detrimental to the voice through its mechanical impact on the vocal folds (Iwahashi, Ogawa, Hosokawa, Kato, & Inohara, 2016). Even though vocal folds can stand more mechanical stress than other tissue and have better capacity to repair small injury effectively, there is a limit for them past which a full-scaled wound healing process would be needed to re-establish normal function (Branski, Verdolini, Sandulache, Rosen, & Hebda, 2005). The injury associated with acute phonotrauma is usually just inflammation that resolves by itself unless the trauma is repeated. In the case of repeated phonotraumatic events, more permanent tissue damage occur and vocal fold nodules, polyps, or cysts can develop (Branski et al., 2005). Coughing during a longer period of time could have effects on the vocal folds that are similar to the effects of repeated phonotrauma.

1.6 Environmental risk factors

Everything that is inhaled passes the vocal folds and irritants can, due to the turbulence created by the laryngeal structures, be deposited there (Levendoski et al., 2014). The vocal fold epithelium is effective in protecting the vocal folds from pollutants if the exposure is short, while longer exposures can disturb the vocal fold epithelial structure (Levendoski et al., 2014). Several other environmental factors have a negative impact on the voice, for example background noise and poor room acoustics (Vilkman, 2004), but these will not be discussed in detail since they are not within the scope of this thesis. The focus will be on

indoor air problems due to moisture damage as a possible environmental risk factor for hoarseness.

1.6.1 Indoor air problems due to moisture damage

Moisture damage is common in Finnish buildings. In a study by Ruotsalainen, Jaakkola, and Jaakkola (1995), 70 % of the 30 day-care centers investigated were damaged by moisture. A leaking roof is a common source of moisture (Gravesen, Nielsen, Iversen, & Nielsen, 1999; Ruotsalainen et al., 1995). Other sources of moisture can be defective plumbing installations, dampness rising from the ground, penetration of cleaning water, and condensation into the building structures (Gravesen et al., 1999). When investigating a random sample of homes in Finland, Koskinen et al. (1999) found moisture problems in 58 % of the school children's homes and in 57 % of the homes of children younger than 7 years. Previous or current moisture damage was observed in 80 % of the random sample of houses from different decades investigated by Nevalainen et al. (1998). The estimated prevalence of moisture damage in school buildings in Finland is 24 % (Haverinen-Shaughnessy et al., 2012). When a structure has been affected by moisture, this promotes microbial growth (Gravesen et al., 1999) and diffusion of chemicals from the building material (Haghighat & De Bellis, 1998; Tuomainen, Seuri, & Sieppi, 2004).

In countries with a moister climate than the Nordic countries, the health symptoms can be caused by moisture induced mite growth (Bornehag et al., 2001). The building material that is most vulnerable to mold is moisture damaged cellulose containing aged organic material (Gravesen et al., 1999), but not only organic materials are susceptible to mold. Inorganic material such as mineral wool can, due to dust and dirt in combination with prolonged moisture exposure, be a surface for mold growth (Gravesen et al., 1999). Volatile organic compounds (VOC) are defined by Williams and Koppman (2007, p.1) as "organic compounds having a vapor pressure greater than 10 Pa at 25 degrees Celsius, a boiling point of up to 260 degrees at atmospheric pressure, and 15 or less carbon atoms". In indoor environments, they are emitted from building materials, office equipment, consumer products, cosmetics, and microbial sources (Nielsen et al., 2007). Emissions of VOC from moisture induced degrading polyvinyl chloride (PVC) floor coverings were in a study by Tuomainen et al. (2004) showed to cause respiratory, dermal, ocular and nasal symptoms. The moisture in the floor of the office building in a study by Tuomainen et al. (2004) stemmed from the concrete that had not been dried enough before it was covered with flooring material. The results of a study by Shu, Jönsson, Larsson, Nånberg, and Bornehag (2014) showed that even exposure to non-damaged PVC flooring in bedrooms during pregnancy or early childhood had a connection to asthma development in children.

A review of previous research showed that moisture damage at home and in public buildings approximately doubles the risk of health effects (Bornehag et al., 2004). The evidence for this being a causal association is, according to a review by Bornehag et al. (2001), strong. Moisture damage in buildings is associated with an increased risk of cough, wheeze (Bornehag et al., 2001; Fisk, Lei-Gomez, & Mendez, 2006), asthma (Bornehag et al., 2001; Fisk et al., 2006; Norbäck, Björnsson, Janson, Widström, & Boman, 1995) and respiratory tract infections (Fisk et al., 2006; Karevold et al., 2006). The results of a population-based cohort study by Jaakkola, Hwang, and Jaakkola (2010) showed that the participating children who lived in moisture damaged homes at baseline or follow-up had a 100 % increased risk of developing allergic rhinitis. If they lived in moisture damaged

homes at both baseline and follow up, the risk increased with almost 200 %. Dampness is also related to more unspecific symptoms as tiredness and headache (Bornehag et al., 2001).

2. Aims of the thesis

The aims of the studies in the present thesis were to:

- investigate the prevalence of hoarseness and vocal symptoms in a normal population of children and in two possible risk groups
- investigate possible risk factors for hoarseness and vocal symptoms in two normal populations and two possible risk groups

The results will be used to:

- provide recommendations on factors that should be included in pediatric voice anamnesis and to, if necessary, recommend voice screening for children in risk groups

Study I

The aim of the first study was to determine the prevalence of hoarseness and frequently occurring vocal symptoms in a normal population of children and investigate possible risk factors associated with a hoarse voice quality.

Study II

The aim of the second study was to compare the frequency of hoarseness in a control group and two risk groups of children that attended an educational setting in a building with indoor air problems due to minor or severe moisture damage. Possible predictors for frequently occurring hoarseness were also explored.

Study III

The aim of the third study was to investigate if allergies and asthma were risk factors for vocal symptoms. Possible risk factors for frequently occurring vocal symptoms were also explored.

Study IV

The aim of the fourth study was to investigate if the number of respiratory tract infections during the first two years of life or the viral etiology of the respiratory tract infections were predictors for a more hoarse voice quality at age 4.

3. Materials and methods

3.1 Participants

The participants in Study I were 217 children from the south and west of Finland. They attended first or second grade of ten different primary schools in the Swedish speaking regions of Finland. They were aged 6:4 years to 9:10 years (mean age 8:3 years). Of the children in Study I, 47.5 % ($n = 103$) were female, and 52.5 % ($n = 114$) male and they all spoke standard Finland Swedish or local dialects of Finland Swedish.

In Study II, the participants were 1857 children aged 6–9 years that attended 57 different day-care centers, preschools, and schools in the east, south and west of Finland. The mean age of the participants was 7.6 years ($SD = 1.1$) with 17 % being 6-year-olds, 29.1 % being 7-year-olds, 23.3 % being 8-year-olds and 27.6 % being 9-year-olds. Of the children, 50.8 % ($n = 944$) were girls and 48.4 % ($n = 899$) were boys. Information on gender was missing for 14 children.

In Study III, the age span of the participants was larger due to the mode of recruitment. The participants were 108 children aged 9 months to 17 years 1 month (mean age 8:4) that were patients at the allergy clinic at Turku University Hospital from 2013 to 2015. In Table 2, a more detailed description of the age distribution of the participants is presented. The gender distribution of the participants was 40.7% ($n = 44$) girls and 59.3% ($n = 64$) boys.

Table 2

The age distribution of the participants in Study III ($N = 108$)

Age group	Participants (n)	%
0 – 1	2	1.9
1:1 – 3:0	11	10.2
3:1 – 5:0	13	12.0
5:1 – 7:0	25	23.1
7:1 – 9:0	9	8.3
9:1 – 11:0	13	12.0
11:1 – 13:0	17	15.7
13:1 – 15:0	10	9.3
15:1 – 17:1	8	7.4

The participants in Study IV were 489 four-year-old children that participated in the multidisciplinary Finnish cohort study Steps to the Healthy Development and Well-being of Children (the STEPS study). The participants were 47.2 % ($n = 231$) girls, and 52.8 % ($n = 258$) boys.

In the general population in Finland 2013, the gender distribution in the age groups 0–4 ($N = 303\ 006$) and 5–9 ($N = 300\ 873$) was 49 % girls and 51 % boys. The gender distribution was the same in the whole age group 0–19 years ($N = 1\ 208\ 567$) (Statistics Finland). The gender distribution in all studies (see Table 3) were similar to the general population in Finland.

Table 3

Summary of the participant characteristics in the four studies

Study	Participants (<i>n</i>)	Age* (Mean)	Gender distribution (F=female, M=male)	Inclusion criteria	Exclusion criteria
I	217	6:4 – 9:10 (8:3)	F: 47.5 % (<i>n</i> = 103) M: 52.5 % (<i>n</i> = 114)		Showed clear signs of having a cold and confirmed this when asked.
II	1857	6 – 9 (7:7)	F: 50.8 % (<i>n</i> = 944) M: 48.4 % (<i>n</i> = 899) Missing: 0.8 % (<i>n</i> = 14)	Age 6 to 9 years. Parents had filled in information on age, which day care center, preschool, or school their child attended, and how often the child had been hoarse during the fall.	
III	108	0:9 – 17:1 (8:4)	F: 40.7% (<i>n</i> = 44) M: 59.3% (<i>n</i> = 64)	Information on both vocal symptoms and voice quality available.	Having a developmental disorder. Undergoing voice mutation.
IV	489	4	F: 47.2 % (<i>n</i> = 231) M: 52.8 % (<i>n</i> = 258)	Participated in the follow-up for at least 1 year. Provided data on respiratory tract infections. Answered the voice quality question in the 4-year questionnaire.	

* Age is given in the format years:months

3.2 Data collection

Study I

In Study I, paper questionnaires were distributed to the parents and teachers of the participating children. In addition to this, voice samples were collected for a perceptual evaluation. Permission for data collection and the use of the data for research purposes was granted from the parents and from the directors of education in the municipalities where the schools were situated.

The parent questionnaire was an adaptation of the questionnaire used by Sederholm, et al. (1995). Fourteen new questions were added to the questionnaire and sixteen questions were modified on wording or scale. Fourteen questions, mainly on musicality, were excluded as they were not within the scope of Study I. The remaining questions concerned family circumstances, living environment of the family, personality and temperament of the child, vocal habits and speaking culture of the family, speech and language development, medical history and statements about the child's voice and vocal habits. The questions were multiple choice or rating questions on a 100 mm horizontal VA-scale. The question on current voice quality was answered on a 100 mm VA-scale with the descriptor completely clear to the left (0 mm) and very hoarse to the right (100 mm). In the parent questionnaire, there were also 21 statements that the parents rated in relation to their child. The statements were adapted from Lee, Stemple, Glaze, and Kelchner (2004) and Simberg, Laine, Sala, and Rönnekaa (2000). Among the statements, there were statements concerning the six vocal symptoms that have been used in previous studies (see eg. Simberg et al., 2000; Simberg, Sala, Laine, & Rönnekaa, 2001). Having frequently occurring vocal symptoms, that is two or more vocal symptoms occurring every week or more often, has in previous research been shown to have a connection to the occurrence of visible changes in the larynx (Sala, Laine, Simberg, Pentti, & Suonpää, 2001). The vocal symptoms were *throat clearing or coughing, the voice gets low or hoarse, the voice becomes strained or tires, difficulty in being heard, sensation of tension, pain or lump in the throat and voice breaks while talking*. The word low in Finnish (*matala*) or Finland Swedish (*låg*) refers to the pitch and not the loudness of the voice. The statements were rated as occurring daily, weekly, less often or not at all. In previous studies where these vocal symptoms have been used, the symptom *loss of voice* has also been included but has not been frequently reported (Simberg et al., 2001).

The teacher questionnaire was shorter and consisted of six questions answered on 100 mm VA-scales with written anchor descriptors at each end. Two questions were on the child's voice, three on the personality and temperament of the child, and one on the peer relationships of the child. The personality and temperament questions were chosen based on the results of previous studies (Green, 1989; Koivusaari, 1998; Roy, Bless, & Heisey, 2000; Sederholm et al., 1995). Both the parent and the teacher questionnaires are included as appendices in the Study I article.

The voice samples were collected during school visits. They were recorded using a Microtrack II Professional 2-channel Mobile Digital Recorder (M-Audio) with the enclosed t-microphone placed on a headset along the child's right cheek with a microphone to mouth distance of about 5 cm. The collected voice samples were a prolonged vowel [a], the sentence: a blue car, a yellow car, a red car (Swe. *en blå bil, en gul bil, en röd bil*) repeated three times, and a task involving narrative/descriptive speech.

The narrative speech was chosen for the perceptual evaluation which was performed by eight evaluators that were Master's students in speech-language pathology. They had received training in perceptual evaluation during a 16-hour course which included lectures, discussions, and practicing perceptual evaluation of different types of voice samples with different rating scales. The perceptual evaluation took place in an ordinary room with all listeners present at the same time. A total of 272 voice samples, 217 original and 55 duplications, were presented from computer speakers of good quality (Trust 1600P 2.1 Soundforce Trust) in a random order. The trained listeners rated hoarseness on a 100-mm VA scale marked completely clear to the left (0 mm) and very hoarse to the right (100 mm).

The intra-rater reliability coefficients for the trained listeners were considered sufficiently high (Table 4) for it to be possible to use the mean of the listener ratings in the data analysis.

Table 4

Intra- and inter-rater reliability for the perceptual evaluation (N = 8)

Listener	Intra-rater r_s	Inter-rater r_s
1	.666**	.714**
2	.806**	.799**
3	.784**	.691**
4	.821**	.688**
5	.706**	.737**
6	.554**	.685**
7	.812**	.606**
8	.684**	.799**

Note. Spearman's rho for intra-rater reliability was calculated by correlating the first and second rating of the same voice sample ($n = 55$). For inter-rater reliability, one listeners rating of a voice sample was correlated with a mean of the other listeners' ratings ($n = 217$).

** Correlation is significant at the .01 level

Study II

The data material was collected 2007–2014 with electronic (98.4 %, $n = 1827$) or paper questionnaires (1.6 %, $n = 30$) in the ongoing nationwide Satakunta-project where the aim is to encourage at least 100 Finnish municipalities to investigate and remediate day care center or school buildings (Putus, 2009). The primary purpose was to evaluate the health status of the children attending day care centers, preschools, and schools before remediating the buildings. Day care centers, preschools, and schools will hereafter be referred to as educational settings. The control group data was collected from parents of children in educational settings with no known indoor air problem due to moisture damage. The data was collected in the educational settings that the municipalities chose to investigate. All children whose parents filled in the questionnaire were included in the original data, while separate inclusion criteria were used for Study II (Table 3). Permission for using the data material for research purposes was obtained from the municipalities where the educational settings were situated and the parents were informed that they by filling in the questionnaire agreed to the data being used for research purposes.

The questionnaire was based on the so called Tuohilampi questionnaire (Susitaival, & Husman, 1996). Similar questionnaires have previously been used by Meklin et al. (2002) and Meklin et al. (2005). The questionnaire consisted of questions regarding the present and previous school and home environment, changes in the general health, infections, doctor diagnosed illnesses, medication and surgery, symptoms in airway, skin, voice, and joints, nausea, fatigue, learning difficulties, and sleeping habits and disorders. The airway symptoms were respiratory, that is dry cough, phlegm cough, wheezing cough, wheeze while breathing, shortness of breath, rhinitis symptoms, that is nasal congestion, watery rhinorrhea, thick rhinorrhea, and the vocal symptom was hoarseness. These questions

were answered on an ordinal four-point scale about the frequency of the symptoms. The alternatives were “never, almost never”, “once or a few times per month”, “every week” and “daily or almost daily”. The first and last two alternatives for the question on hoarseness were merged into two groups that were called “seldom/never” and “every week or more often”. The question on the frequency of laryngitis was answered on an eight-point ordinal scale from “once” (1) to “eight times or more often” (8) and all other questions were multiple choice questions. When the parents filled in the questionnaire, they were asked to answer the questions on symptoms for both spring and fall term, either during the same academic year or the same calendar year. The data for the fall was used for the analysis to reduce the risk of seasonal allergies affecting the results.

Based on the degree of moisture damage in the building (minor, severe, or no moisture damage) where the children had attended an educational setting, they were coded into three groups. No moisture damage ($n = 114$) meant no need for repair or only cosmetic repairs. Minor damage ($n = 677$) meant visible moisture damage and need for repair between 0.1 m^2 and $<1 \text{ m}^2$ in one or more classrooms, and severe damage ($n = 1066$) meant visible moisture damage and need for repair of $\geq 1 \text{ m}^2$ in one or more classrooms.

Study III

The paper questionnaire used in Study III was distributed to the parents of new pediatric patients 2013–2015 at the allergy clinic at Turku University Hospital. The primary purpose of the questionnaire was to obtain information about the patient in connection to their visit at the allergy clinic. An overview of the questions in the questionnaire is presented in a table in the Study III article. Permission for using the data for research purposes was granted by the Hospital District of Southwest Finland (T05/041/14), and a notification of data use was sent to the data protection ombudsman (2518/4225/14).

The questionnaire consisted of questions on allergy in the family and allergic symptoms, the home and day care/school environment, general health of the child, asthma or cough symptoms, eczema, personality traits and temperament, vocal symptoms, and voice quality. The questions on voice quality, personality, and temperament were answered on 100 mm VA-scales. The scale for voice quality was marked completely clear to the left (0 mm) and very hoarse to the right (100 mm). The vocal symptoms that the parents rated the occurrence of were: *throat clearing or coughing*, *the voice gets low or hoarse*, *the voice becomes strained or tires*, *difficulty in being heard*, *sensation of pain, tension, or lump in the throat* and *voice breaks and loss of voice*. The statements were rated as occurring daily, weekly, less often or not at all. Children who had two or more vocal symptoms occurring every week or more often were coded as having frequently occurring vocal symptoms. The other questions in the questionnaire were multiple choice, yes/no questions, or open-ended questions.

The variable called inhalant allergy was composed of the answers to the questions on asthma symptoms, or rhinitis and/or eye symptoms because of dust, animals, and pollen. If the parents reported some of the above mentioned types of symptoms from one of the three allergen groups, the child was coded as having inhalant allergy. Generally, dust mites and mold are also regarded as allergens in inhalant allergy (Krouse & Mabry, 2003), but because the parents had not been asked specific questions about the reactions to dust mites and mold in the questionnaire, these were not included.

Study IV

The questionnaires used in Study IV were filled in by the parents of the children participating in the cohort study Steps to the Healthy Development and Well-being of Children (the STEPS study). The children were born between January 2008 and April 2010 (Lagström et al., 2012). Data was collected in a systematic follow-up with questionnaires being filled in at 4 months, 8 months, 13 months, 18 months, 24 months, 3 years, and 4 years. All but the four year questionnaire were paper questionnaires. The four year questionnaire was mainly distributed electronically and few parents (less than 10 %) opted for a paper version of the questionnaire.

In the four year questionnaire, the parents were asked questions on their child's development, language, health, everyday life and environment. They were asked to rate their child's voice quality ("What is your child's voice like (when the child is healthy)?") on an eleven-point equal-appearing interval scale where 0, placed on the left hand, was defined as *completely clear* and 10, placed on the right hand, was defined as *very hoarse*. The equal-appearing interval scale was chosen because of the technical properties of the web survey software where the electronic questionnaire was created. Questions on time use for a specific activity were answered by filling in a number and all other questions were multiple choice.

In addition to these questionnaires, data was also collected through a diary filled in by the parents when the child was 0–2 years old. In the diary, the parents documented respiratory tract infections, physician visits, and medications of the child (see Lagström et al. (2012) for further details). Information about physician visits and test results from pharyngeal swab tests were also used.

For a subgroup of the children, nasal swabs were taken at the onset of a respiratory tract infection, either by the family or by a physician. The nasal swabs were analyzed, as described in more detail in Toivonen, Schuez-Havupalo et al. (2016), by polymerase chain reaction and antigen tests for rhinovirus, respiratory syncytial virus, enterovirus, influenza A and B viruses, parainfluenza viruses, metapneumovirus, and adenovirus. Data on emergency department visits and hospitalization of the child was obtained from the electronic registry of the Hospital District of Southwest Finland.

If the child was documented to have rhinitis or cough, with or without fever or wheezing, this was entered as an episode of acute respiratory tract infection. This could be documented in the diary by the parents, or by a physician. Because of the varying follow-up time between different participants, the number of observations of the variables listed in Table 5 (except for the variables voice quality and day care attendance) are given as observations per year to be comparable.

Table 5

Descriptions of the variables that were considered when constructing the model (N = 489)

Variable	Data available, n (%)	Distribution of yes/no answers	Mean (SD)	Range	Number of answers with a value > 0
Voice quality	489 (100 %)		1.54 (2.5)	0–10	
Day care attendance from 13 months to 4 years	489 (100 %)	Yes: 59 No: 430			
Number of RTI episodes	489 (100 %)		6.3 (2.6)	0–14.5	487
Rhinovirus infections	468 (95.7 %)		2.1 (1.4)	0–8	439
Respiratory syncytial virus infections	468 (95.7 %)		0.2 (0.3)	0–1.5	146
Enterovirus infections	468 (95.7 %)		0.1 (0.2)	0–1	84
Influenza infections	468 (95.7 %)		0.02 (0.1)	0–0.94	18
Parainfluenza virus infections	468 (95.7 %)		0.1 (0.2)	0–1	46
Human metapneumovirus infections	468 (95.7 %)		0.03 (0.1)	0–1	26
Adenovirus infections	468 (95.7 %)		0.01 (0.06)	0–0.5	7
Number of hospitalizations due to RTI	489 (100 %)		0.04 (0.2)	0–2	31
Number of laryngitis episodes	489 (100 %)		0.1 (0.27)	0–2	67

Note 1. Voice quality was measured at age 4, and day care attendance at five occasions between age 13 months and 4 years. The other variables were measured during the first two years of life. These variables are listed as observations per year.

Note 2. RTI = respiratory tract infections

3.3 Statistical analyses

In studies I-III, IBM SPSS Statistics 20 (Armonk, NY) was used for the statistical analyses. Nonparametric tests were generally used in all four studies. When exploring the connection of hoarseness and possible binary risk factors in Study I, the Mann-Whitney U-test was used

and the two-tailed exact significance value was reported. When the response alternatives were more than two, the Kruskal-Wallis test was used. When data from VA scales were correlated, the Spearman's correlation coefficient was reported. Intra-rater reliability was calculated by correlating the listeners' first and second ratings of the duplicated voice samples with each other. The inter-rater reliability was calculated by correlating the ratings given by one listener with a mean of the other listeners' ratings. Because the intra-rater reliability was high, only the first rating of a voice sample was used when calculating the inter-rater reliability.

In Study II, the associations between how often a child was hoarse and the degree of moisture damage in the day care center, preschool, or school they had attended were calculated using cross-tabulations and the chi-square test. Predictors for the child being hoarse every week or more often were explored using multiple logistic regressions.

In Study III, Spearman's correlation coefficient was used. The connection between binary and continuous data was explored using the Mann-Whitney *U* test and the two tailed exact significance value was reported. For questions with two answer alternatives for both variables, the Pearson's chi square test was used and valid percent was reported.

In Study IV, IBM *SPSS Statistics* 21 software (IBM, Armonk, NY) was used for the statistical analyses. A linear regression analysis was used to investigate if gender, daycare attendance from 13 months to 4 years, the number of respiratory tract infection episodes, the number of hospitalizations due to respiratory tract infections, the number of laryngitis episodes, the number of respiratory syncytial virus infections, and the number of rhinovirus infections were significant predictors for a more hoarse voice quality. The analyses were performed both as univariate, with only one predictor variable, and as multivariate, controlling for gender and day care attendance from 13 months to 4 years.

4. Results

4.1 Prevalence of hoarseness and frequently occurring vocal symptoms

In Study I, the prevalence of hoarseness in a normal population of children was 12 % ($n = 26$) based on the point of discontinuity of the ranked means of the perceptual evaluations (Figure 1). The point of discontinuity was determined by visual inspection by two experienced voice researchers involved in the study. More boys (15.8 %, $n = 18$) than girls (7.8 %, $n = 8$) were hoarse, but the difference was not significant ($U = 5142.5$, $z = -1.577$, *ns*). In Study I, parents also reported the frequency of six vocal symptoms on a four-point ordinal scale. The parents of 6% ($n = 13$) of the children reported that their children had frequently occurring vocal symptoms, i.e. two or more vocal symptoms occurring every week or more often. One of the vocal symptoms that the parents filled in was "the voice gets low or hoarse". This vocal symptom was reported as occurring every week or more often in 5.5 % ($n = 12$) of the children.

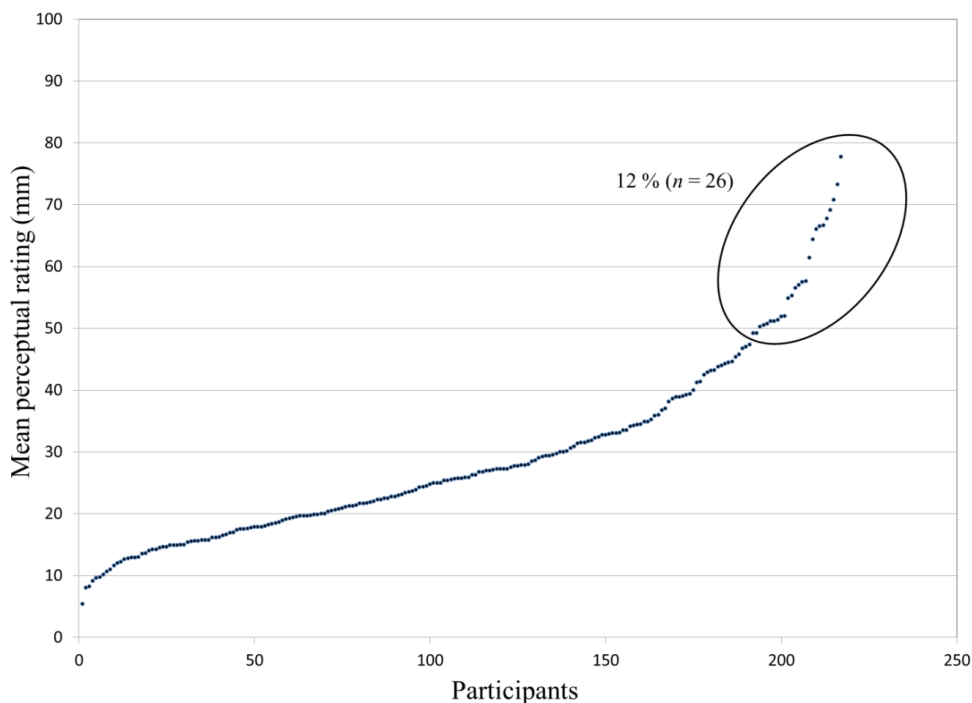


Figure 1. The ranked means of the hoarseness ratings given by the trained listeners (N = 217).

In Study II, an ordinal four-point scale was used to measure how often a child was hoarse. In the control group, 3.5 % ($n = 4$) children were hoarse every week or more often. In the group that had attended an educational setting in a building with minor moisture damage, 6.4 % ($n = 43$) were hoarse, and in the group that had attended an educational setting in a building with severe moisture damage, 9.3 % ($n = 99$) children were hoarse every week or more often.

In Study III, the parents of children with allergy and/or asthma reported the frequency of the same vocal symptoms as in Study I. Of the children, 18.2% ($n = 18$) had frequently occurring vocal symptoms.

4.2 Risk factors

No significant gender difference in voice quality rating or frequency of vocal symptoms was found. In Study I, there was no significant gender difference in voice quality, neither when comparing the girls (median rating 24.75 mm) and the boys (median rating of 26.88 mm) with each other ($U = 5142.5$, $z = -1.577$, ns) nor when comparing the gender distribution of the group we characterized as hoarse with the gender distribution of the other group ($\chi^2(1) = 3.302$, $p = 0.093$). The mean value on the voice quality scale for the whole group in the children with allergy and/or asthma in Study III was 18.3 mm ($SD = 22$). The mean value for girls was 19.1 mm ($SD = 24.3$) and the mean value for boys was 17.7 mm ($SD = 20.3$). For the purpose of comparison with Study I, the median was also calculated. The median was 5 mm for girls, and 11 mm for boys (8.5 mm for the whole group). In Study II

where the frequency of hoarseness was measured, there was no significant gender difference [$\chi^2 (1) = 1.58$; $p = 0.226$; Cramer's $V = 0.029$]. In Study IV, gender was not a significant predictor for a more hoarse voice quality (Table 6).

For girls in the normal population in Study I, heavy voice use as an infant had a significant connection to hoarseness ($U = 422$, $z = -2.13$, $p = .032$). In the children with allergy and/or asthma in Study III, heavy voice use as an infant did not have a significant connection to frequently occurring vocal symptoms ($U = 555.5$, $z = -1.09$, $p = 0.276$). For boys in Study I, being the youngest sibling had a significant connection to current voice quality ($U = 1052$, $z = -2.60$, $p = .009$). Teachers had in Study I been asked to rate the personality and temperament of their pupils. A low teacher rating of the degree of maturity correlated significantly with current voice quality ($r_s = .187$, $p = .006$).

Attending a pedagogical setting in a building with moisture damage can be seen as a risk factor for hoarseness based on the results of Study II where the association between the degree of moisture damage in the building and how often the children were hoarse was significant ($\chi^2 (2) = 8.1$; $p = 0.018$; Cramer's $V = 0.07$).

In Study II, dry cough (Wald (3) = 35.73, $p < .001$), phlegm cough (Wald (3) = 9.35, $p = .025$) and nasal congestion (Wald (3) = 46.25, $p < .001$) were significant predictors for being hoarse every week or more often when controlling for the other variables in the multiple logistic regression model. In Study III, having had cough that lasted for more than 4 weeks had a significant connection to frequently occurring vocal symptoms ($\chi^2 [1] = 6.257$, $P = 0.012$).

The results regarding the connection between asthma, asthma medication and hoarseness or vocal symptoms were inconclusive. Of the children with asthma in Study I, 31.8 % ($n = 7$) had two or more vocal symptoms. Of the children who were using asthma medication on a daily basis, 35.7 % ($n = 5$) had two or more vocal symptoms but equally many of the asthma medication group had no vocal symptoms (35.7 %, $n = 5$) or one vocal symptom (28.6 %, $n = 4$). In Study III, there was no significant connection between asthma and frequently occurring vocal symptoms (Fischer's exact test, $p = .75$). There was no significant connection between using the asthma medicine Ventoline ($\chi^2 [1] = 0.005$, $p = 0.941$) or inhaled corticosteroids (Fisher's exact test, $p = 0.687$) and having frequently occurring vocal symptoms. Of the children with inhalant allergy in Study III, 28.6% ($n = 14$) had frequently occurring vocal symptoms. The connection between inhalant allergy and frequently occurring vocal symptoms was significant ($\chi^2 [1] = 7.04$, $p = 0.008$).

In Study IV, the number of hospitalizations due to respiratory tract infections was a significant predictor for a more hoarse voice quality both independently and when controlling for gender and day care attendance (Table 6).

Table 6

The results of univariate and multivariate linear regression analyses investigating the relationship between the listed variables and voice quality

	Univariate					Multivariate*				
	B	Std error B	Beta	p	Adj R ²	B	Std error B	Beta	p	Adj R ²
Gender	-.248	.229	-.049	.280	.000	-.245	.229	-.048	.286	.002
Day care attendance from 13 months to 4 years	.468	.351	.060	.184	.002	.464	.351	.060	.187	.002
Number of RTI episodes	.080	.044	.083	.068	.005	.073	.044	.076	.096	.006
Number of hospitalizations due to RTI	1.922	.622	.139	.002**	.017	1.866	.623	.135	.003**	.018
Number of rhinovirus infections	-.139	.081	-.079	.086	.004	-.139	.081	-.079	.086	.007
Number of respiratory syncytial virus infections	.713	.391	.084	.069	.005	.699	.390	.083	.074	.008
Number of laryngitis episodes	.502	.420	.054	.232	.001	.479	.420	.052	.255	.002

Note. *Controlling for gender and daycare attendance from 13 months to 4 years (yes/no), RTI = respiratory tract infections.

5. Discussion

In this thesis, risk factors for and the prevalence of hoarseness and vocal symptoms was investigated in four different populations. The children that were defined as hoarse had a voice that in a perceptual evaluation had been assigned a VAS rating above the value at the point of discontinuity of the ranked means (Figure 1). Frequently occurring vocal symptoms was defined as having two or more of a set of vocal symptoms every week or more often. Data was collected with parent (studies I – IV) and teacher questionnaires (Study I). Study I also included perceptual evaluation by eight trained listeners and in Study IV, nasal swab samples were taken at the onset of respiratory symptoms and health symptoms were recorded by the parents in a diary.

5.1 Prevalence of hoarseness and frequently occurring vocal symptoms

The prevalence of hoarseness of 12 % in this thesis most closely resembles the prevalence of 14 % obtained by Sederholm (1995) whose methods also were most similar to the methods used in this thesis. Despite that Koivusaari (1998) also investigated Finnish

children, the prevalence of 28 % was much higher than the 12 % in this thesis. A possible explanation for this could be that Koivusaari (1998) also included resonance disorders while these were not included in the present thesis. The rating of vocal symptoms that was used in Study I and III has not been used in a pediatric population before, but in two previous studies with university students, 17 % had frequently occurring vocal symptoms (Ohlsson et al., 2012; Simberg, Sala, & Rönnekaa, 2004). This is similar to the results of Study III, but not Study I. A crucial difference between the studies by Ohlsson et al. (2012) and Simberg et al. (2004) and the studies in this thesis was that the students filled in the questionnaire themselves, while parent proxy was used in this thesis. If we compare the results of Study I and Study III with each other, more of the children with allergy and/or asthma had frequently occurring voice symptoms, but if we compare the results in this thesis with the results of Ohlsson et al. (2012) and Simberg et al. (2004), they are quite similar. Because the rating of vocal symptoms has not been used in a pediatric population before, the fairest comparison is probably between Study I and III, based on which more children with allergy and/or asthma (18.2%) than children in the normal population (6 %) had frequently occurring vocal symptoms. Of the children that had inhalant allergy in Study III, 28.6% had frequently occurring vocal symptoms. This is in line with the results of previous studies with adult participants where participants with inhalant allergy had more vocal symptoms (Simberg, Sala, et al., 2009) and a higher degree of vocal dysfunction (Randhawa et al., 2010).

In previous studies about parent and child agreement in questionnaires regarding health related quality of life, the parent child agreement has been fairly good (Brunner et al., 2004), but diminishes with increasing age of the child (Rajmil et al., 2013). The fact that the children in Study III were part of a population seeking help for allergy and/or asthma, while the children in Study I were a normal population could have had an impact on the results (Upton et al., 2008). In a study by Rietveld, Van Beest, and Everaerd (2000), the importance of the context of the testing, in this case for cough in persons with asthma, was investigated. It was concluded that patients with asthma cough more often in a situation that they associated with asthma than if the situation was stripped of cues on what was being investigated.

A reasonable comparison to the frequency of hoarseness in Study II could be the frequency of the vocal symptom “the voice gets low or hoarse” in Study I. This vocal symptom was frequently occurring in 5.5 % of the children in the normal population in Study I, while 9.3 % of the children who had attended an educational setting in a building with indoor air problems due to severe moisture damage were hoarse every week or more often. Unfortunately, it is not possible to exclude that some of the homes or schools of the children participating in Study I had indoor air problems due to moisture damage since this was not included in the questionnaire. When collecting voice data in future studies, this would be important information.

5.2 Risk factors

Either gender was not identified as a risk factor in the studies included in this thesis. In a previous study where the voice use in boys and girls in a day care environment was investigated using voice accumulators, no significant gender differences in fundamental frequency, vocal intensity or phonation time were found (Nygren, Tyboni, Lindström, McAllister, & Doorn, 2012). Laryngeal and airway anatomy also seems to be similar before

puberty (Fitch & Giedd, 1999; Vorperian et al., 2005) and is more related to age, height, and weight than to gender (Dalal et al., 2009). Despite this, it is possible to perceptually distinguish prepubertal girls from prepubertal boys (Amir et al., 2012; Perry et al., 2001). This indicates that there are other auditory features that provide clues about the gender of a child.

In the normal population in Study I, heavy voice use as an infant had a significant connection to hoarseness for girls. The younger the child, the more immature structure of the vocal folds (Boseley & Hartnick, 2006), and it could be possible that the mechanical strain that heavy voice use (i.e. screaming) puts on the vocal folds is more detrimental to the voice the earlier it occurs. It is also possible that a child who has been loud as an infant continues to be a loud toddler and so on. However, this does not explain why the correlation was significant for girls, but not for boys. There are some results that suggest that voice disorders are more persistent in girls than in boys. In a study by De Bodt et al. (2007) on the evolution of vocal fold nodules, the voice disorder persisted after puberty in significantly more girls than boys. Almost half the girls still had vocal fold nodules, compared to 7 % of the boys. The results of a study by Martins et al. (2016) also showed that nodules were far more common in boys up to the age of 12, while, after that, nodules were more common in girls and women. In the children with allergy and/or asthma in Study III, heavy voice use as an infant did not have a significant connection to frequently occurring vocal symptoms. A possible explanation for this could be that there were other factors related to the airway reactions from the allergy and/or asthma or the treatment that had a greater impact in these children.

A low teacher rating of the degree of maturity and the degree of hoarseness was significantly correlated which fits in with the results of Green (1989) where the children with vocal nodules scored higher on immature behaviors. The role of personality and temperament was not the main focus of this thesis, and should be further studied with questionnaires that have been validated for that purpose (for some suggestions, see e.g. Maćkiewicz & Ciecuch, 2016).

Being the youngest sibling had a significant connection to the degree of hoarseness for boys, possibly because a younger sibling wants to make himself heard among older siblings. On the other hand, the results of a study by Tuzuner, Demirci, Oguz, & Ozcan (2017) showed that having younger siblings correlated with the use of a loud speaking volume at home. Having older siblings increases the risk of recurrent respiratory tract infections (Toivonen, Karppinen et al., 2016) and cough is a common symptom of respiratory tract infection (West, 2002; Widdcombe, 1995). Cough was a significant predictor for being hoarse every week or more often in Study II, and having had cough that lasted for more than 4 weeks had a significant connection to frequently occurring vocal symptoms in Study III.

The pressure with which the vocal folds are pressed together when coughing is significantly higher than the pressure when phonating (Shaker, Dua, Ren, Xie, Funahashi, & Schapira, 2002). In voluntary coughing, the vocal folds make contact at a higher velocity and with a higher impact stress, than at voice onset when phonating (Iwahashi et al., 2016). This results in a higher risk for damage of the tissue in the larynx (Iwahashi et al., 2016). The vocal fold epithelium can be injured when the vocal folds are intensely used, and this can weaken the protective function of the epithelium (Levendoski et al., 2014). An altered epithelial structure is, in turn, associated with different kinds of vocal fold pathologies (Levendoski et al., 2014). The connections between vocal symptoms and cough found in

Study II and III could be associated with damage to the epithelium. The majority of the participants in the four studies were prepubertal children whose vocal folds were still developing and maturing. They lack the stabilizing vocal ligament (Hartnick et al., 2005) that prevents the vocal folds from overstretching (Titze, 1994). It could be possible that this makes cough even more detrimental to the voice.

The connection between degree of moisture damage and the frequency of hoarseness was not strong which might reflect that most cases of hoarseness are multifactorial and caused by a combination of different factors. In a previous study by Meklin et al. (2005), more children were hoarse (28–30 %), but in that study, older participants possibly affected by puberty were also included. Since Meklin et al. (2005) viewed hoarseness as a health symptom among others, the effect of puberty was not discussed. To increase knowledge about if and how the voice quality is affected by indoor air problems due to moisture damage, more voice research should be done. If indoor air problems due to moisture damage affects the children's voices, and this in turn can affect how they are perceived and what they can do, both for the time being and in the future, this is one more argument to make sure that the buildings that the children spend time in are in good condition. We want the children to leave the education system better equipped for the future, not worse.

In Study II, nasal congestion was a significant predictor for being hoarse every week or more often. The results of a study by Filiz, Selçuk, and Baran (In press) indicated a similar connection between allergic rhinitis and vocal dysfunction. In the study by Filiz et al. (In press), the children with allergic rhinitis had higher scores on the pediatric voice handicap index compared to the healthy controls. One could assume that such a connection would be via cough caused by post-nasal drip, but Kemp (2006) argues that in children, this commonly held assumption should be re-evaluated. Instead, Kemp (2006) suggests that both cough and nasal discharge are part of the same pathological process, not that one causes the other. It could thus be possible that the nasal congestion is just a symptom of a disease process with other symptoms that puts strain on the vocal folds.

The results regarding the connection between asthma, asthma medication and hoarseness or vocal symptoms were inconclusive. In previous studies with adult participants, the use of ICS has been associated with hoarseness (Buhl, 2006; Gallivan, Gallivan, & Gallivan, 2007; Ihre et al., 2004; Spantideas, Drosou, Bougea, & Assimakopoulos, 2017) and the types of ICS that are included in the medicines Symbicort and Flixotide that the children used are those most frequently associated with dysphonia (Spantideas et al., 2017). On the other hand, in inadequately managed asthma that is later treated with ICS, the treatment can actually improve the voice quality through improved lung function and reduced cough (Balter, Adams, & Chapman, 2001). In the study by Balter et al. (2001), the follow-up time was only 4 months and they discuss that it is possible that longer use could lead to a deterioration of the voice quality. In Study III, no significant association between the use of ICS and having frequently occurring vocal symptoms was found. It is possible that the participating children could have been using the ICS in a way that lowers the risk for dysphonia: inhaling the medicine correctly, using a low dose, and rinsing the mouth and oropharynx after inhalation (Spantideas et al., 2017). The asthma medicine Ventoline, where salbutamol is the active ingredient, was more commonly used among the children in Study III. Ventoline use was not significantly associated with frequently occurring vocal symptoms which could be expected as no voice-related side effects are listed in the consumer information.

In Study III, no significant connection between having an asthma diagnosis and having hoarseness and vocal symptoms was found. The explanation for this could be that all participating children had some kind of allergy and/or asthma and that no control group was included. The internal difference in the group could have been too small for any significant connections regarding asthma to occur.

The connection between inhalant allergy and frequently occurring vocal symptoms was significant. Inhalant allergy was in Study III defined as having asthma symptoms, rhinitis and/or eye symptoms from dust, animals, and pollen. Both asthma symptoms and rhinitis are associated with a reaction in the mucosa in the airways. It could be possible that this mucosal reaction includes the vocal folds. The fact that the number of hospitalizations due to respiratory tract infections was a significant predictor for a more hoarse voice quality could also be attributed to the above mentioned possible connections airway mucosa reactions, and mechanical strain from cough. If hospitalization is necessary, this is also a sign of a more severe respiratory tract infection and some children that have been hospitalized may also cry and use a loud voice more due to the environment and the severity of the illness. Additionally, the vocal fold epithelial barrier could be damaged by the virus and bacteria that cause the infections, and this in turn could make the vocal folds more susceptible to damage.

5.3 Methodological considerations

Different scales for measuring voice quality were used in the studies. In Study I and III, we asked about both the frequency of different vocal symptoms on a four-point ordinal scale, and about the voice quality on a VAS. In Study II, we used a four-point ordinal scale, and in Study IV an eleven-point equal-appearing interval (EAI) scale. The end points of the VA scale and the eleven-point EAI scale was marked *completely clear* and *very hoarse* while the subject of the four-point ordinal scale questions was how often the children experienced hoarseness (Study II) and a selection of other vocal symptoms (Study I and III). This means that the same difficulties that appear in voice research in general, the use of different scales and differences in what is being measured, also appears within the research of this thesis. What was measured was largely decided by the context where the questionnaire was being distributed. Voice research was the main purpose only in Study I, while the data collection in studies II & IV was for multiple research purposes, and the data collection in Study III mainly for clinical purposes. It was important that the voice questions that we used were quick to fill in since they, in Study II and III, were included in questionnaires with numerous other questions, and in Study IV were part of a cohort study questionnaire. Study I was, for practical reasons, the only study that included perceptual evaluation by trained listeners. This was not feasible in the other three studies because of the participant numbers, and the vast geographical area or time-frame of the data collection. In Study IV, the intention was to use the same VA scale as in Study I, but due to the technical properties of the web survey software used, this was not possible. Since a VAS also can be viewed as an interval scale (Wevers & Lowe, 1990), we used the eleven-point EAI scale instead.

The above mentioned compromises made it more relevant to look at connections and correlations to risk factors rather than to compare the prevalence of hoarseness in different groups. This is also a relevant approach when considering that all children that we consider hoarse might not experience this as a problem, while those whose voice quality we do not

perceive as affected still might be bothered by vocal symptoms. This does not mean that adults, e.g. parents, educators, and health care personnel, should give up the responsibility for the children's vocal health – sometimes adults have to make decisions for the well-being of the children – but that a better approach might be to first ask about the level of activity and participation limitations in the child's life and then plan the intervention around that. The age of the child is also a factor that affects the choice of intervention. Regardless of age, a first step after a thorough examination by a phoniatician or ENT physician to rule out medical conditions that requires other types of intervention, could be to try to eliminate the known risk factors.

Determining the cut-off point between normal voice quality and hoarse voice quality in study I turned out to be more challenging than originally thought. The intention was to use the same method as Sederholm (1995) where the intersection between two regression lines was used to determine the point of discontinuity. However, the intersection is possible to affect by selecting which values to include in which line, and the method for selection of values is described neither in Sederholm (1995) nor in Sederholm et al. (1993) where the same method was used. The cut-off point is described qualitatively in Sederholm et al. (1993) as the point at which the pattern of the line changes so that the scatter is smaller below the point than above. Based on this, and since the use of regression lines also seemed to be based on a certain degree of subjectivity, it was concluded that a simple method of visual inspection could be used. Based on the experience from the four studies included in this thesis, the prevalence of vocal symptoms would perhaps be a better measurement. This incorporates a functional viewpoint and, if the voice user him- or herself is being asked, the personal experience of how the voice functions in everyday life. This does not mean that a perceptual voice quality evaluation would be unnecessary, but that the results on a continuous scale could be more useful for finding connections to risk factors rather than for determining prevalence.

In all four studies, we asked an adult about the voice of the child. There are results from interview studies that indicate that children are able to answer questions on physical and socio-emotional aspects of their voice from a young age (Cohen & Wynne, 2015; Connor et al., 2008; Verduyck et al., 2011). These studies involved fewer participants, 24 – 40 children, than our studies did. Our participant groups consisted of 108, 217, 489, and 1857 children and to interview all of them personally would not have been feasible. If the children instead would have been presented with a standard questionnaire, there could have been a risk that they would have misinterpreted some of the questions. Verduyck et al. (2011), who interviewed children with and without dysphonia, reported that the children had some difficulties in distinguishing the voice from other aspects of speech, and to grasp the exact nature of the voice difficulties they were asked about. Therefore, an adult proxy approach was considered most appropriate in the studies in this thesis. We did not ask which of the parents that had filled in the questionnaire, which in retrospect would have been of interest, since mothers and fathers of children with dysphonia have been shown to rate their children's voices differently (Amir, Wolf, Mick, Levi, & Primov-Fever, 2015). Another limitation was that the parents in study II were asked to rate the frequency of hoarseness and other symptoms, either for spring or for fall, from memory. In the questionnaire, they were asked about the symptoms for both spring and fall, one being further away in time than the other. The questionnaires were filled in at different times during the year, which means that some parents reported the symptoms for fall from memory and some reported the symptoms for spring from memory. This has likely led to

the parents either under- or over-reporting the symptoms, possibly depending on the current health status of their child.

There are questionnaires that have been adapted for parent proxy use in a pediatric population available, for example the pediatric voice handicap index (pVHI; Zur, Cotton, Kelchner, Baker, Weinrich, & Lee, 2007), the Pediatric Voice-Related Quality-of-Life (PVRQOL; Cohen & Wynne, 2015; Boseley, Cunningham, Volk, & Hartnick, 2006), and the pediatric voice outcome survey (VOS; Hartnick, 2002). Of these, the pVHI seems to be most frequently used. In Swedish, the second most spoken language among our participants, there is an unpublished Master's thesis on the adaptation of the pVHI to a Swedish speaking child population (Bylund & Eriksson, 2010). Adaptations have also been done in Arabic (Shoeib, Malki, Mesallam, Farahat, & Shehata, 2012), Chinese (Liu et al., 2018), Dutch (Veder et al., 2017), French (Oddon, Boucekine, Boyer, Triglia, & Nicollas, 2017), Italian (Schindler et al., 2011), Korean (Park et al., 2012), and Spanish (Sanz, Bau, Arribas, & Rivera, 2016) but there does not seem to be any published adaptations in Finnish.

5.4 Conclusions

The main findings from the studies in this thesis were:

- a prevalence of hoarseness of 12 % in a normal population of children. The prevalence of frequently occurring vocal symptoms was 6 %.
- a prevalence of frequently occurring vocal symptoms of 18.2 % in children with allergy and/or asthma.
- that indoor air problems due to moisture damage can contribute to a frequently occurring hoarseness. Of the children who had attended an educational setting in a building with indoor air problems due to severe moisture damage, 9.3 % were hoarse every week or more often.
- that cough seem to be connected to vocal symptoms and hoarse voice quality.
- that nasal congestion, inhalant allergy, heavy voice use during infancy (for girls), being the youngest sibling (for boys), and the number of respiratory tract infections that have led to hospitalization could be listed as risk factors for vocal symptoms and hoarse voice quality.
- that no significant gender differences in the prevalence of vocal symptoms or voice quality were found.

Recommendations based on this would be that:

- cough should be treated and the underlying reason for the cough, whether it is a pathological process or something in the environment, should be targeted.
- children with vocal symptoms should be referred to a speech-language pathologist where risk factors for vocal symptoms and hoarseness should be identified and, if possible, eliminated.
- children with allergy and/or asthma should be screened for vocal symptoms.

5.5 Suggestions for future research

In future child voice studies, valid and reliable instruments for measuring the children's own opinions about their voice should be developed in Finnish. Since defining hoarseness and voice problems will always, at least at some stage, be a matter of someone's subjective

opinion, we should primarily ask for the opinion that matters the most, namely that of the voice user. If the hoarseness or the vocal symptoms bother the voice user, then it should be regarded as a problem. One potentially useful instrument could, for example, be the pVHI. In Swedish, this work has been initiated by Bylund and Eriksson (2010) and their translation of pVHI should also be tested in a Finland Swedish population before being used for research purposes in Finland. The participant groups in future studies should be comprised of children of a more similar age and all children who are close to the age of onset of puberty should be excluded.

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